Treatment of Depression

Definition of Major Depressive Disorder

Unipolar major depression (major depressive disorder) is diagnosed in patients with:

a history of at least one major depressive episode

no history of mania or hypomania

the depressive episode is not caused by medications or concurrent another medical conditions

A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms:

depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide

at least one of the symptoms must be depressed mood or anhedonia.

Treatment Phases

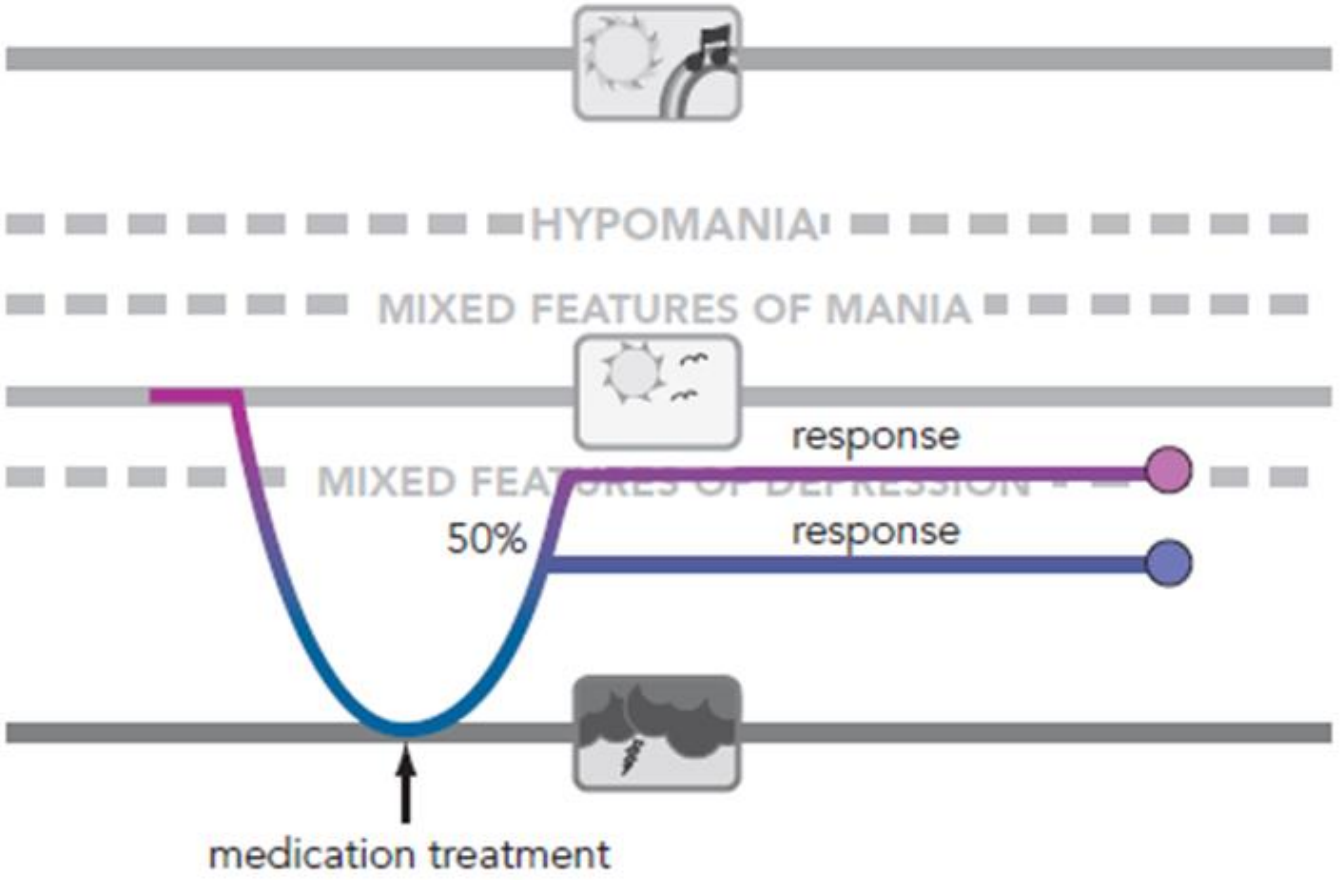
- Acute
- Continuation
- maintenance (if appropriate)

The goals of the acute phase are to achieve

remission (resolution of all symptoms) and

restore functioning

Response in depression



Remission in depression

When treatment of major depressive episode results in removal of essentially all symptoms, it is called remission for the first several months

Remission and recovery are now the goals when treating patients with depression.

Resolution of the depressive syndrome, which can be operationalized by a depression rating scale score less than or equal to a specific cutoff that defines the normal range.

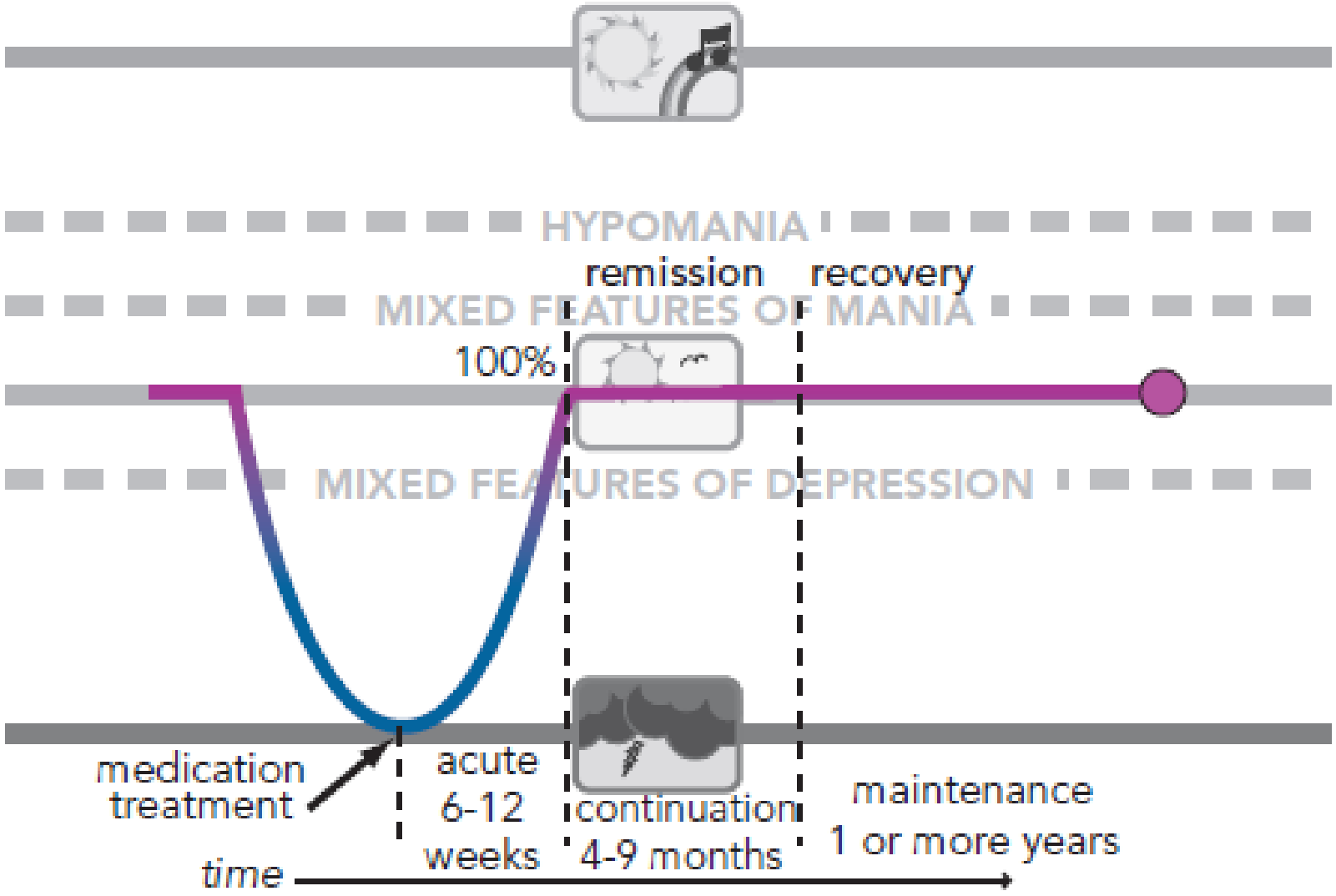
As an example, studies using the 17 item Hamilton Rating Scale for Depression or the Montgomery-Asberg Depression Rating Scale often define remission as a score ≤7, while studies using the Patient Health Questionnaire – Nine Item (PHQ-9) often define remission as a score <5.

Remission ends with either relapse or recovery.

Recovery

Recovery occurs when patients remain well for a period of time exceeding the interval that defines remission.

Recovery can be indefinite or can end with recurrence.

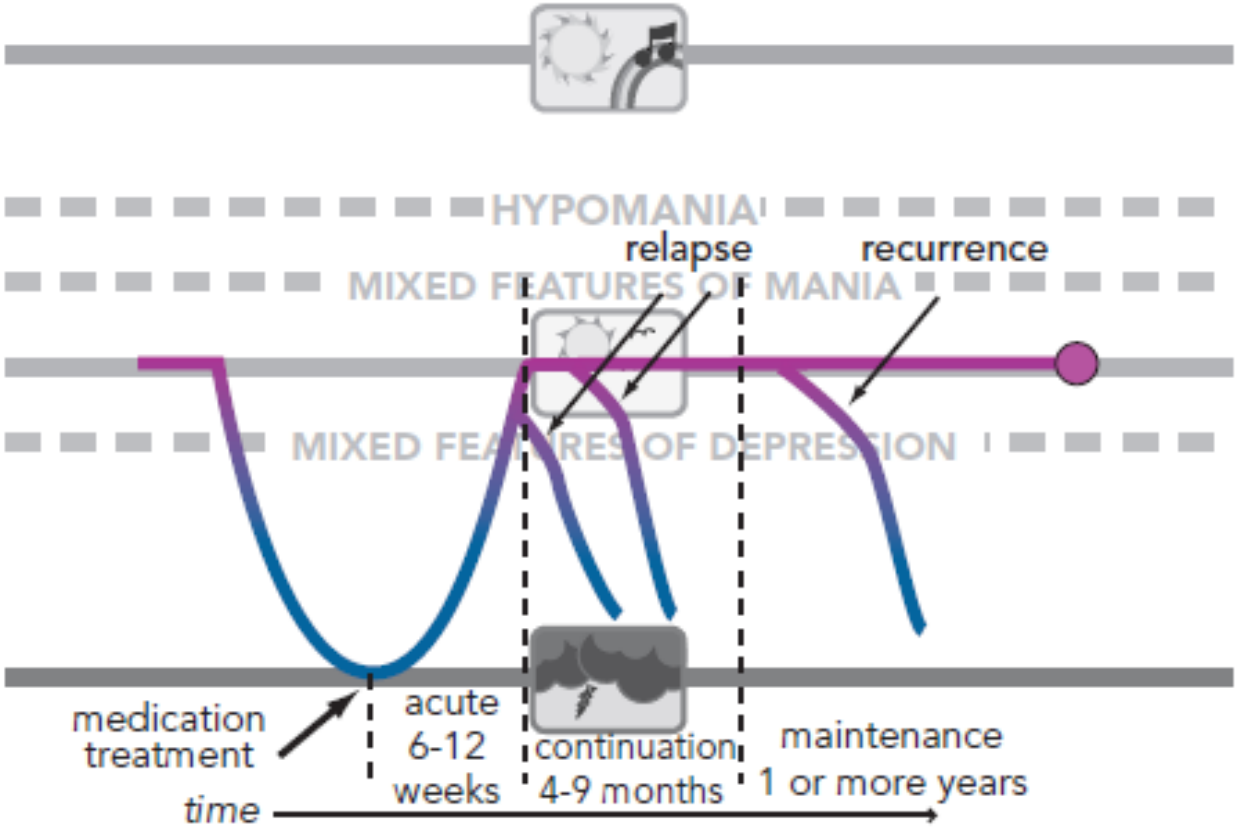

HYPOMANIA
remission
recovery
MIXED FEATURES OF MANIA
100%
MIXED FEATURES OF DEPRESSION
medication
treatment
acute
6-12
weeks
continuation
4-9 months
maintenance
1 or more years
time

Relapse and Recurrence

When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a relapse.

When depression returns after a patient has recovered, it is called a recurrence.

Relapse and recurrence in depression



Pharmacotherapy of MDD

first-generation antidepressants

Tricyclic and tetrcyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, nortriptyline, protriptyline, and trimipramine, maprotiline)

Monoamine oxidase inhibitors (MAOIs) (isocarboxazid, moclobemide (not available in the United States), phenelzine, transdermal selegiline, and tranylcypromine)

TCAs and monoamine oxidase inhibitors are typically not used as initial treatment because of concerns about safety (particularly in overdose) and adverse effects.

Second-generation antidepressants

Selective serotonin reuptake inhibitors (SSRIs) (Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline, Paroxetine)

Serotonin-norepinephrine reuptake inhibitors (Desvenlafaxine, Venlafaxine, Duloxetine, Levomilnacipran, Milnacipran)

Atypical antidepressants (Agomelatine, Bupropion, Mirtazapine)

Serotonin modulators (Nefazodone, Trazodone, Vilazodone, Vortioxetine)

Efficacy

Studies that suggest antidepressants (including SSRIs) differ in their efficacy include a network meta-analysis of 117 randomized trials (mean duration eight weeks), which compared 12 second-generation antidepressants in nearly 26,000 patients with unipolar major depression. The investigators concluded that escitalopram and sertraline showed the best combined profile of efficacy and acceptability, based upon the findings that:

- Response (reduction of baseline symptoms ≥50 percent) was more probable with escitalopram, mirtazapine, sertraline, and venlafaxine, compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine.

- Discontinuation of treatment for any reason was less probable with citalopram, escitalopram, and sertraline, compared with other antidepressants.

asecond meta-analysis (93 randomized trials, >20,000 patients with unipolar major depression) evaluated 13 second-generation antidepressants and concluded that there were no substantial differences in efficacy and discontinuation rates.

In contrast to the first network meta-analysis, the second one excluded trials with a high risk of bias and open label designs.

●Most of the differences between antidepressants that were found in the first study were not replicated in the second study.

●Although the second study did find a few statistically significant differences, these were judged to be small and not clinically relevant. As an example, improvement was greater with escitalopram than citalopram, but the average difference on the Montgomery-Asberg Depression Rating Scale which ranges in score from 0 to 60 points, was 1.5 points.

Randomized trials have found no evidence that one antidepressant is superior in preventing relapse or recurrence.

Onset of Action

Onset of action may be faster with mirtazapine than other antidepressants.

A systematic review identified seven randomized trials that found response occurred sooner with mirtazapine than citalopram, fluoxetine, paroxetine, or sertraline.

However, all of the studies were funded by the manufacturer of mirtazapine, and after four weeks, response rates were generally comparable.

selecting a drug is based upon other factors

- Safety
- Side effect profile
- Specific depressive symptoms
- Comorbid illnesses
- Concurrent medications and potential drug-drug interactions
- Ease of use (eg, frequency of administration)
- Patient preference or expectations
- Cost
- Patient response to antidepressants during prior depressive episodes
- Family (eg, first degree relative) history of response to antidepressants

As an example, bupropion is useful for patients who prefer to avoid sexual dysfunction or want treatment for comorbid tobacco dependence,

citalopram and escitalopram may be less likely to cause drug-drug interactions, and

mirtazapine is often not used for patients who want to avoid weight gain.

In addition, bupropion may be less effective for patients with co-occurring anxiety.

Patient response to antidepressants during prior episodes and family history of response to antidepressants are often used in choosing an antidepressant.

Therapeutic use of side effects

- Choosing more sedating antidepressants (such as mirtazapine or paroxetine) for more anxious, depressed patients
- more activating agents (bupropion) for more psychomotor-retarded patients is not as helpful as one might think.
- For example, any short-term benefits with paroxetine or mirtazapine on symptoms of anxiety or insomnia may become liabilities over time.
- Some practitioners use adjunctive medications, such as hypnotics or anxiolytics, combined with antidepressants to provide more immediate symptom relief or to cover those side effects to which most patients ultimately adapt.

Treatment of specific depressive disorders

- Clinical types of major depressive episodes may have varying responses to particular antidepressants or drugs other than antidepressants.
- Antidepressants with dual action on both serotonergic and noradrenergic receptors may have greater efficacy in melancholic depressions.
- We can treat patients with seasonal winter depression with light therapy.

major depressive episodes with psychotic features

- Treatment of major depressive episodes with psychotic features may require a combination of an antidepressant and an atypical antipsychotic.
- Several studies have also shown that ECT is useful for this indication— perhaps more effective than pharmacotherapy.

Atypical depression

- For those with atypical symptom features, strong evidence exists for the effectiveness of MAOIs.
- SSRIs and bupropion are also of use in atypical depression.

Comorbid Disorders

- the successful treatment of an OCD associated with depressive symptoms usually results in remission of the depression.
- Similarly, when panic disorder occurs with major depression, medications with demonstrated efficacy in both conditions are preferred (e.g., tricyclics and SSRIs).
- In general, the non-mood disorder dictates the choice of treatment in comorbid states.

Substance use

- Concurrent substance abuse raises the possibility of a substance-induced mood disorder, which must be evaluated by history or by requiring abstinence for several weeks.
- Abstinence often results in remission of depressive symptoms in substance-induced mood disorders.
- For those with continuing significant depressive symptoms, even with abstinence, an independent mood disorder is diagnosed and treated.

General medical conditions

- General medical conditions are established risk factors in the development of depression.
- The presence of a major depressive episode is associated with increased morbidity or mortality of many general medical conditions (e.g., cardiovascular disease, diabetes, cerebrovascular disease, and cancer).

- Understanding a patient's prior treatment history is essential because an earlier response typically predicts future responses.
- A documented failure on a properly conducted trial of a particular antidepressant class is grounds to choose an agent from an alternative class.
- The history of a first-degree relative responding to a particular drug is associated with a positive response to the same class of agents in the patient.

Selecting a specific antidepressant

For patients with unipolar major depression whose initial treatment includes antidepressants, SSRIs were suggested.

SSRIs are the most widely prescribed class of antidepressants

Early improvement and response

Among patients with unipolar major depression who start antidepressants, improvement is often apparent within one to two weeks

Early improvement during initial treatment of depression with antidepressants may predict eventual remission .

A pooled analysis of 41 randomized trials (n >6000 patients with unipolar major depression who were generally treated for six weeks) found that early improvement (reduction of baseline symptoms within the first two weeks of treatment ≥20 percent) was a sensitive predictor of eventual remission (range 87 to 100 percent, depending upon the specific treatment)

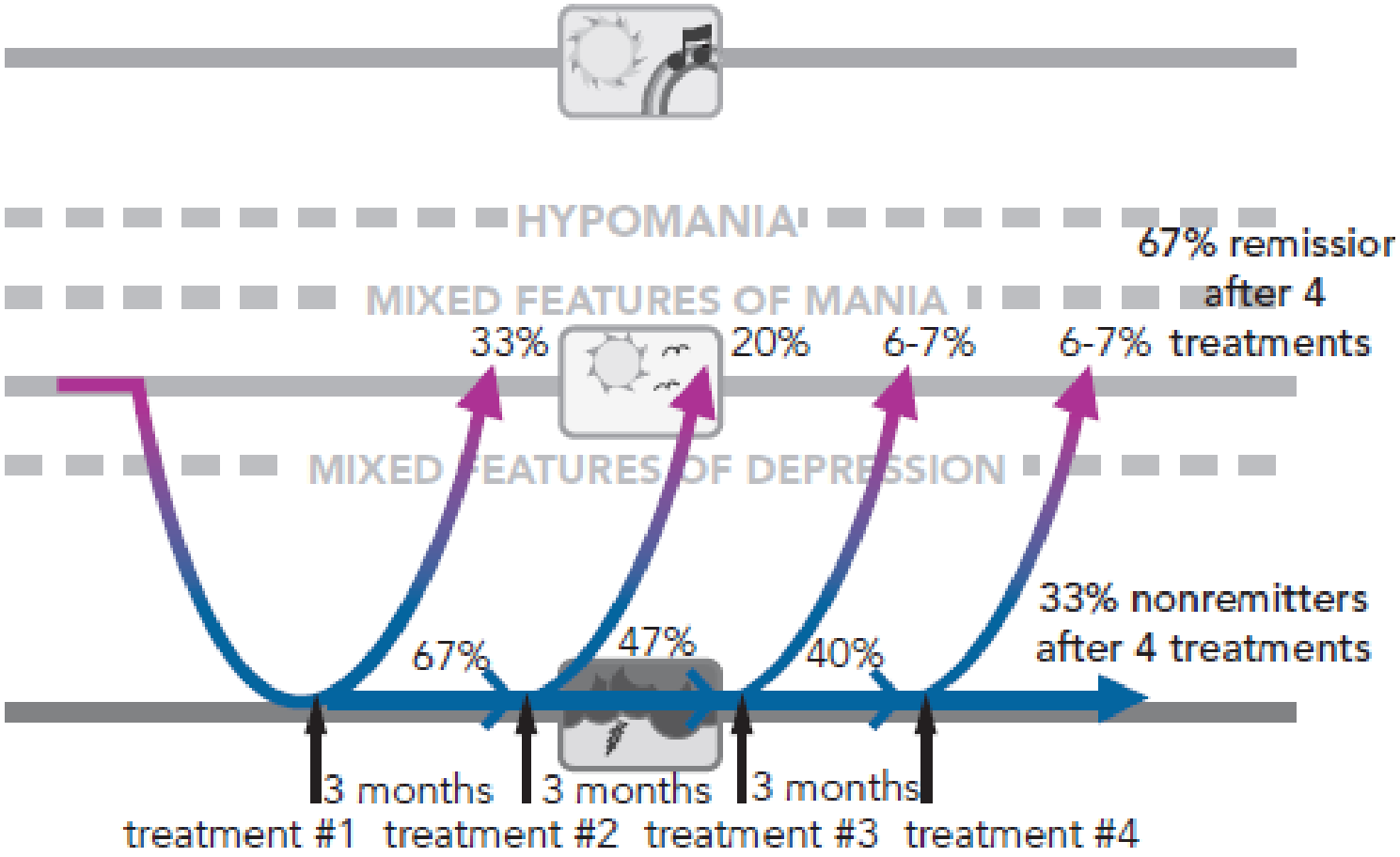
Among all the patients who remitted, more than 90 percent were early improvers.

Duration of an adequate trial

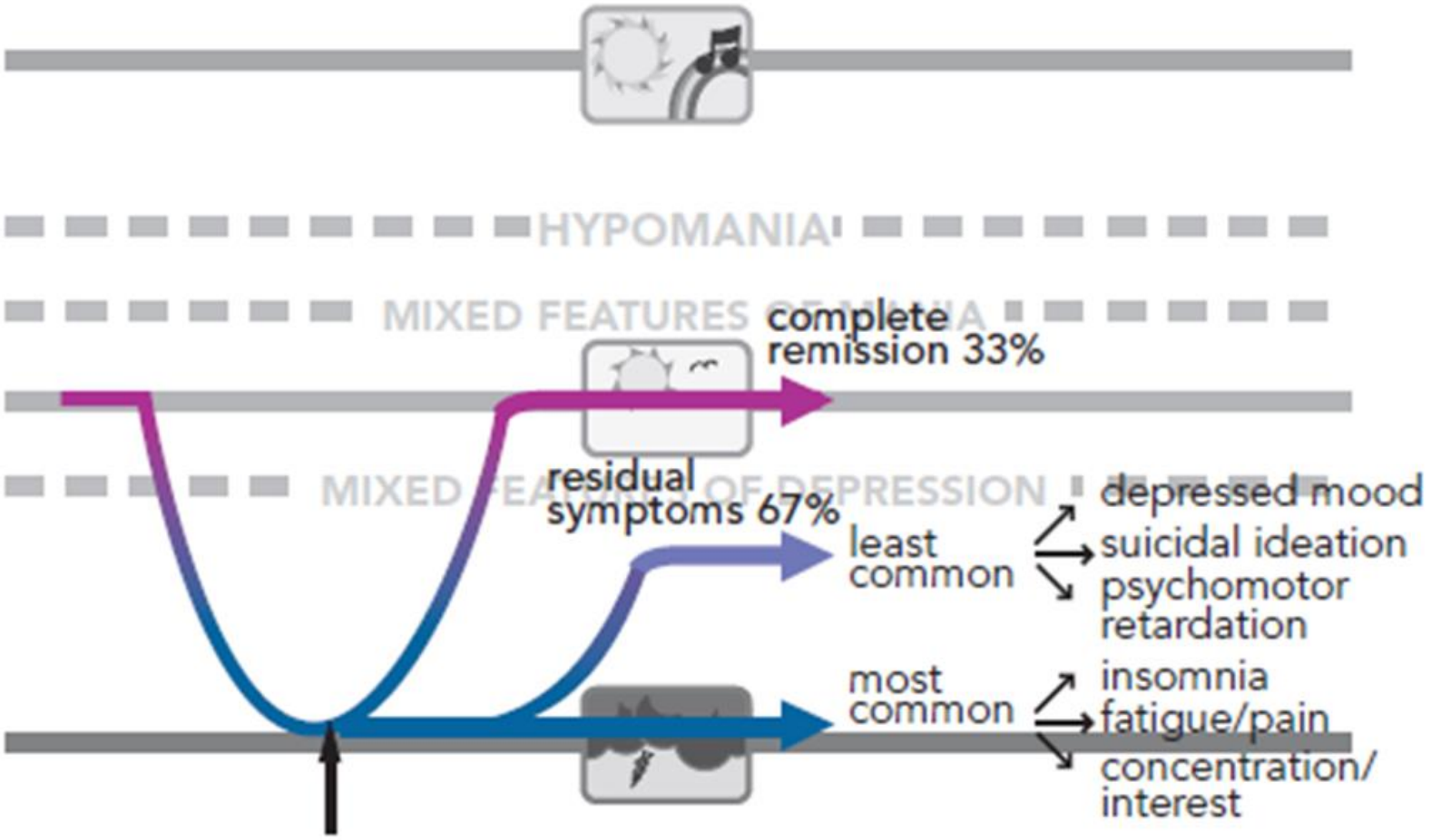
We generally treat unipolar major depression for 6 to 12 weeks before deciding whether antidepressants have sufficiently relieved symptoms.

for patients who show little improvement (eg, reduction of baseline symptoms ≤25 percent) after four to six weeks, it is reasonable to administer next-step treatment

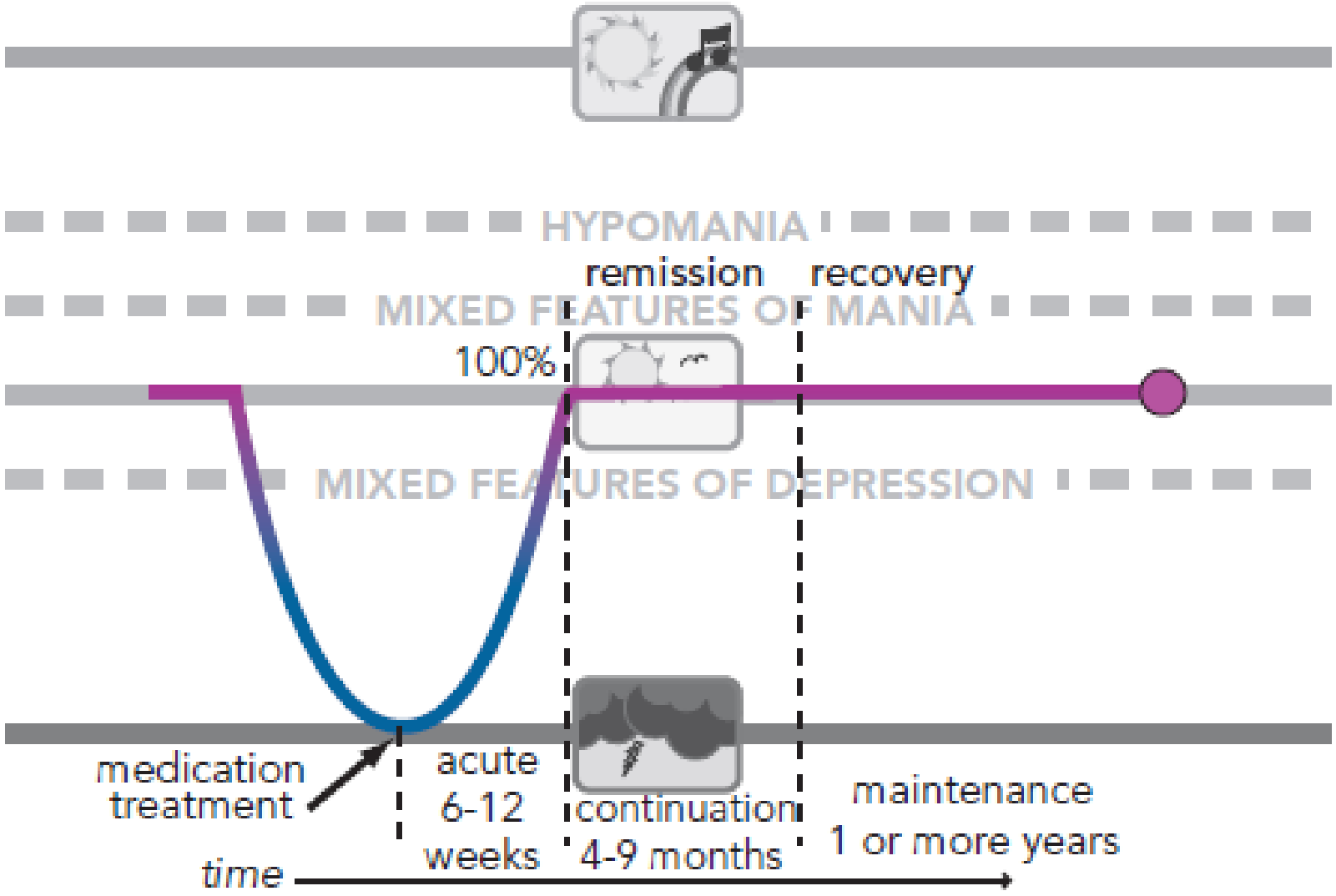
What Proportion of Unipolar Major Depressive Episodes Remit?



What Are the Most Common Residual Symptoms in Nonremitters?



Continuation Phase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Failure to achieve complete remission (recovery) has major adverse consequences including the following

- increased risk of relapse and treatment resistance
- persistent functional impairment
- sustained risk of suicide
- worsened morbidity of other psychiatric conditions and medical disorders

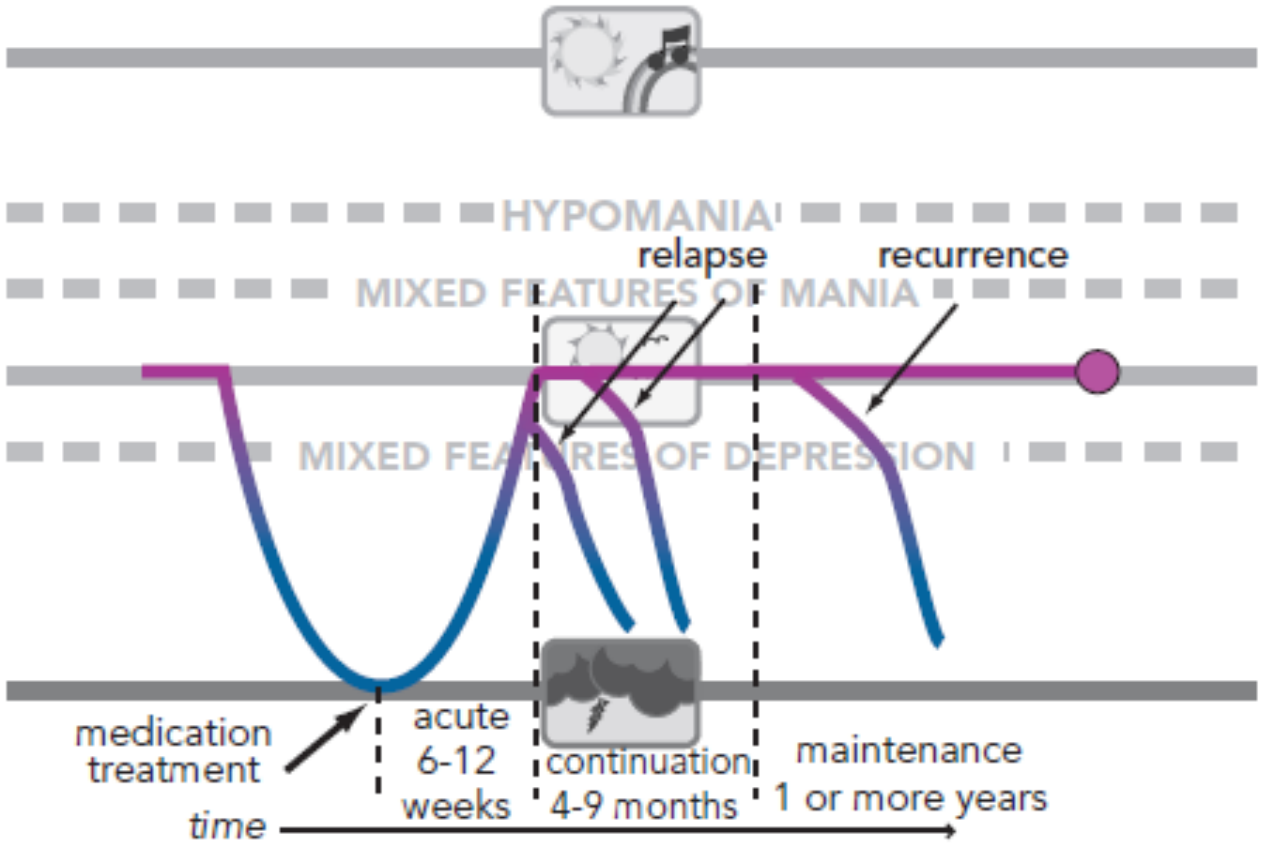
This phase should last approximately 6 months following full remission of the acute episode.

Discontinuation

- Then, the patient in whom the risk for recurrence is low should be gradually tapered from treatment over a period of 1 to 3 months.
- Rapid discontinuation of virtually all antidepressants, including those with long half-lives, tends to be associated with symptomatic relapse.

Maintenance phase

The aim of the maintenance phase is to prevent recurrence



- Maintenance treatment with antidepressants is effective in reducing the number and severity of recurrences.
- One study concluded that when episodes are less than 2.2 years apart, we should recommend prophylactic treatment.
- Another factor suggesting prophylactic treatment is the seriousness of previous depressive episodes.
- Episodes that have involved significant suicidal ideation or impairment of psychosocial functioning may indicate that the risk of stopping treatment is too considerable.

Acute Treatment Failure

Patients may not respond to medication, because

(1) they cannot tolerate the side effects, even in the face of an excellent clinical response;

(2) an idiosyncratic adverse event may occur

(3) the clinical response is not adequate

(4) the wrong diagnosis has been made.

- Most (but not all) patients who ultimately respond fully show at least a partial response by the fourth week, assuming an adequate dose.
- A "partial response" is defined as at least a 20 to 25 percent reduction in pretreatment depressive symptom severity.
- Patients who have not even a partial response in that time likely need a change of treatment.
- More extended periods—8 to 12 weeks or longer—are needed to define the ultimate degree of symptom reduction achievable with a medication.
- Approximately half of patients require a second medication treatment trial because the initial treatment is poorly tolerated or ineffective.

Selecting Second Treatment Options

- When the initial treatment is unsuccessful, switching to an alternative treatment or augmenting the current treatment is a standard option.
- The choice between switching from the single initial treatment to a new single treatment (as opposed to adding a second treatment to the first one) rests on

-the patient's prior treatment history,

-the degree of benefit achieved with the initial treatment,

- and patient preference.

Augmentation strategies

- augmentation strategies are helpful with patients who have gained some benefit from the initial treatment but who have not achieved remission.

augmentation options

- Several antipsychotics, most notably quetiapine and aripiprazole, are effective for augmentation.
- Lithium augmentation is also effective for augmenting both SSRIs and TCAs.
- There are also positive studies of thyroid hormone. However, this strategy is rarely used in clinical practice owing to the need for ongoing monitoring and potential adverse effects.
- other agents including: bupropion, buspirone, lamotrigine, methylphenidate, and pindolol; however, these have limited placebo-controlled data.

Switching

When switching from one monotherapy to another, the usual suggestion is to pick a medication in a different class.

For example, we might switch from an SSRI to an SNRI.

However, when putting these assumptions to the test, it is difficult to find any advantage for any particular strategy.

For example, in the landmark STAR*D study, which remains one of the most extensive studies of treatment strategies following initial failure, although medication switches were modestly helpful, both switches within and outside a class were equally effective.

Switching to a different treatment

- SNRIs (eg, venlafaxine)
- Atypical antidepressants (eg, bupropion or mirtazapine)
- Tricyclic antidepressants (eg, imipramine or nortriptyline)
- MAOIs (eg, phenelzine or tranylcypromine)

it is reasonable to use these drugs in a different sequence, or to switch to a different SSRI at any point in the sequence

Cross-tapering

For treatment-resistant patients who are switching antidepressants, we generally cross-taper, that is, taper and discontinue the failed medication over one to two weeks at the same time that another antidepressant is started and titrated up

clinicians should be aware of overlapping side effect profiles, as well as potential drug-drug interactions such as the serotonin syndrome

NOVEL PHARMACOLOGIC AGENTS

- Ketamine
- Brexanolone

Other Somatic Treatments

- **NEUROSTIMULATION**
  - Vagal Nerve Stimulation
  - Transcranial Magnetic Stimulation
- **ELECTROCONVULSIVE THERAPY**
- **PHOTOTHERAPY**
- **SLEEP DEPRIVATION**